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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,004	02/12/2001	Bassil I. Dahiyat	A-67229-6/RFT/RMS/RMK	1900

7590 11/18/2004
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EXAMINER

BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/782,004

Applicant(s)

DAHIYAT ET AL.

Examiner

Michael Borin

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12, 13 and 21-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12, 13 and 21-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2 IDSs</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

Response to restriction requirement filed 07/29/2003 is acknowledged. Applicant elected, with traverse, Group I, claims 12,13,21-24. The traverse of the restriction requirement is noted but is moot in view of cancellation of the claims drawn to non-elected groups.

Claims 12,13,21-24 are under examination.

Information Disclosure Statement

1. Applicants' Information Disclosure Statements filed 09/04/2001, 10/07/2002, and 07/08/2003 have been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Specification: Incorporation by reference

2. The attempt to incorporate subject matter related to utilizing forcefield calculation into this application by referring to plurality of references cited in paragraph bridging pages 14 and 15 is improper because the way of calculating forcefield is essential material to describe the claimed method. There is plurality of various ways of forcefield calculations, as evidenced by various references cited in specification, and, unless acknowledged otherwise by applicant, it is essential

Art Unit: 1631

which method of forcefield calculation is employed in the claimed method. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 U.S.P.Q. 157 (C.C.P.A. 1973); *In re Hawkins*, 486 F.2d 579, 179 U.S.P.Q. 163 (C.C.P.A. 1973); and *In re Hawkins*, 486 F.2d 577, 179 U.S.P.Q. 167 (C.C.P.A. 1973).

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 12, 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons.

A. Claim 12, step (a): The claim addresses input of coordinates. However, it is not clear what coordinates are meant: global coordinates of the entire protein, or coordinates of each residue or coordinates of backbone. Do "coordinates" define

Art Unit: 1631

two-dimensional or three-dimensional protein structure? Although there is one mention of the term "coordinates" in the specification (p.8, line 23)¹, it addresses some "scaffold" protein, rather than "target" protein of the instant claims. Consequently, the specification does not provide a standard for ascertaining the meaning of "coordinates", and one of ordinary skills in the art would not be reasonably appraised of the scope of the invention.

B. Claim 12, step (b). The term "calculation" in regard to forcefield calculations is vague and indefinite. Forcefield calculations can be made using various approaches and each approach can consist of a plurality of calculations. See, for example, references cited in paragraph bridging pages 14 and 15, or Ulrich et al (Proteins: Structure, Function, and Genetics, 27,367-384, 1997) who teaches (p. 367, second paragraph):

"Some forcefields can be tightly connected to an underlying physical basis in that they should in some ways be an average over physical terms. Alternatively, a force field may be statistical in nature"

Therefore, it is not clear which "calculation": is singled out by the claim.

C. Claim 12: It is not clear what is relation of method step (c) to other method steps: the subsequent step (d) utilizes "primary variant positions" which are defined in step (b), so there is no nexus between step (c) and other method steps.

¹ In general, specification seems to be an assortment of embodiments not necessarily related to each other, much less to the claimed method.

Art Unit: 1631

D. Claims 21-24: The claims are directed to *in vitro* steps; however, as the claims are dependent on claim 12 which is drawn to *in silico* method, the nexus between *in vitro* and *in silico* parts of the method are not clear.

Claim Rejections - 35 U.S.C. § 101/ 112-1

4. Claims 12, 21-24 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. The specification at page 5, lines 13-24 discloses that the present invention is directed to methods of using computational screening of protein sequence libraries to select smaller libraries of protein sequence that can be used in a number ways. For example, the proteins can be actually synthesized and experimentally tested in the desired assay, improved function and properties. Similarly, the library can be additionally computationally manipulated to create a new library which then itself can be experimentally tested. However, creating a library for further screening or testing is not a utility for the method. A library is similar a composition in nature that has to undergo screening to isolate and identify a product. The court in *Brenner v. Manson*, 148 U.S.P.Q. at 689 expressed the opinion that chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in U.S.C.

Art Unit: 1631

101, which requires that an invention must have either an immediately apparent or fully disclosed "real world " utility. The court held that:

The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.. . a patent is not a hunting license. . . is not a reward for the search, but compensation for its successful conclusion. Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use or testing "

Brenner, 148 USPQ at 696.

The instantly claimed method provide for generating a secondary library of as yet undetermined structure, function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the secondary library was, as of the filing date, useful for any industrial or any pharmacological uses. Until some actual and specific significance can be attributed to the secondary library or even the compounds present the library, an artisan would be required to perform additional experimentation in order to determine how to use the generated secondary library. Thus, there was no immediate "real world " utility as of the filing date. Because any potential pharmacological utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in any specific and practical form. The specification does not disclose substantial interpretation for the result; and none is known in the art. In order for generated library to be useful, as asserted, for any pharmacological use, there must be a well- established or disclosed claimed library correlation or relationship between the and a disease or disorder. The secondary library of as yet

Art Unit: 1631

undefined structure allegedly generated from the claimed method does not have a specific and substantial or real-world utility well-established utility.

5. Claims 12,21-24 are also rejected under U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12,21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no description in the specification of a method that includes all method steps a), b), c), d) as claimed. Specification seems to be a collection of description off alternative approaches in protein modeling, rather than description

Art Unit: 1631

of a particular method, e.g., method as instantly claimed. Forcefield calculations are recited in passing on pages 14-15 of specification; these calculations are addressed not as the main step in generating primary library, but rather as a supplemental technique which can be used in addition to other methods to optimize conformation of a sequence within a computational method (p. 14-15). Also, example 2, describes combination of protein design automation (PDA) used in conjunction with generation of probabilities for residues; however, as PDA may utilize a number of different scoring functions (see specification, p. 1, fourth paragraph) it is not possible to identify whether forcefield calculations in particular have been utilized in this example. The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; *see also Lockwood v.*

Art Unit: 1631

American Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). Similarly to *In re Wilder*, 736 F.2d 1516 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 1209 (1985) the specification did "little more than outline] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate." There is no showing of a single embodiment demonstrating generation of a secondary library by cumulating method steps as claimed. The reader can certainly appreciate the goal but establishing goals does not make a patent.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a

Art Unit: 1631

nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 12,21-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,403,312 in view of Wang et al (Pub. Med ID 8862547; Protein Engineering, 9(6),479-484, 1996) or Ulrich et al (Proteins: Structure, Function, and Genetics, 27,367-384, 1997).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '312 claims teach method for generating secondary library comprising steps a), c), and d) of instant claim 12, as well as synthesis of peptides addressed in the instant claims 21-24. Although the claims of '312 are not specifically drawn to utilizing forcefield calculations to generate primary library, use of forcefield calculations would be obvious to one skilled in the art because it is well known that such calculations allow to optimize conformation of a peptide sequence within a computational method and are thus desirable in order to obtain energy-efficient conformations which can be useful in creating secondary library. For example, Wang et al demonstrate that force field calculations evaluate compatibility between amino acid residues and their environment and are thus useful as a guide in protein engineering and as an effective scoring matrix in protein modeling. Ulrich et al teach that force field

Art Unit: 1631

calculations are effective in discriminating between native structures and their misfolded alternatives. See abstracts.

8. Claims 12, 21-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-21 of copending Application No. 09/927790 in view of Wang et al (Pub. Med ID 8862547; Protein Engineering, 9(6),479-484, 1996) or Ulrich et al (Proteins: Structure, Function, and Genetics, 27,367-384, 1997).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claims in 09/927790 claims teach method for generating secondary library comprising steps a), c), and d) of instant claim 12, as well as synthesis of peptides addressed in the instant claims 21-24. Although the claims of '312 are not specifically directed to utilizing forcefield calculations to generate primary library, they recite use of a scoring function to generate set of optimized primary variant sequences. Use of forcefield calculations as a scoring function would be obvious to one skilled in the art because it is well known that such calculations allow to optimize conformation of a peptide sequence within a computational method and are thus desirable in order to obtain energy-efficient conformations which can be useful in creating secondary library. For example, Wang et al demonstrate that force field calculations can be used as an effective scoring matrix in protein modeling, and evaluate compatibility between amino acid residues and their environment. Ulrich et al teach that force field calculations are effective in discriminating between native structures and their misfolded alternatives. See abstracts.

Art Unit: 1631

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1631

Claim 12 is rejected under 35 U.S.C. 102(e) as being anticipated by Lacroix et al (US 2002/0072864; filing date 08/31/1999).

The claims are drawn to method for generating a secondary library of target protein comprising:

- a) inputting coordinates of said protein into a computer;
- b) utilizing forcefield calculation to generate primary library comprising a plurality of primary variant amino acid residues at primary variant positions;
- c) computationally generating a probability distribution table of variant amino acid residues in a plurality of said primary variant positions; and
- d) combining a plurality of said primary variant amino acid residues to generate a secondary library of secondary variant proteins.

US 2002/0072864 teaches computer-based method for macromolecular engineering wherein the method comprises steps of

- a) inputting coordinates of said protein into a computer (see, e.g., claims 12,13);
- b) using various force field calculations (see sections 5.4.1; 5.8.1; 5.9.2)
- c) identifying probability of having rotamers (i.e., amino acid residues) from a system of possible rotamers (see section 5.9.2, paragraph [0164]).

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed or fully envisioned by the teaching of the references cited above.

Claims 21-24 are rejected under 35 U.S.C. 103(a) as obvious over Lacroix et al (US 2002/0072864; filing date 08/31/1999). The reference teaches synthesizing candidate structure(s) (see, e.g., claim 158). Although the reference does not teach specifically PCR method, such conventional method of protein synthesis would be an obvious choice to an artisan.

Prior art made of record

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Altshul et al (Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. Nucleic Acid Research, 1997, 25, 3389-3402) teaches generation of probabilities for residues to be located in a certain position of a protein (see page 3396, first full paragraph).

Conclusion.

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1631

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

11/12/04